

Figure 1

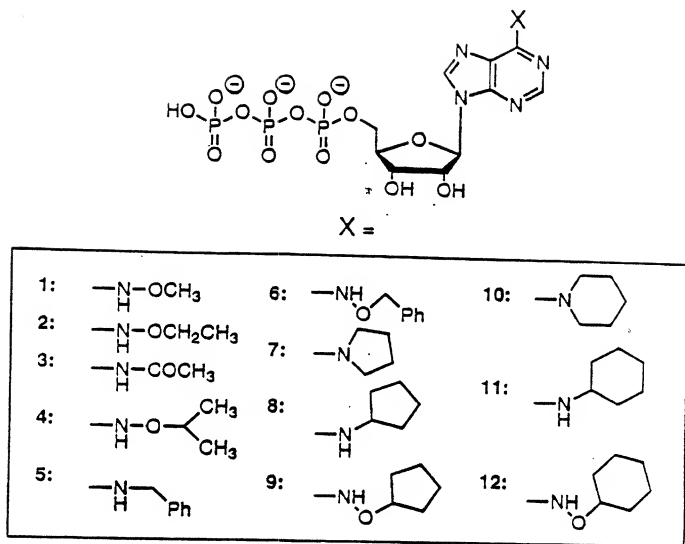


Figure 2

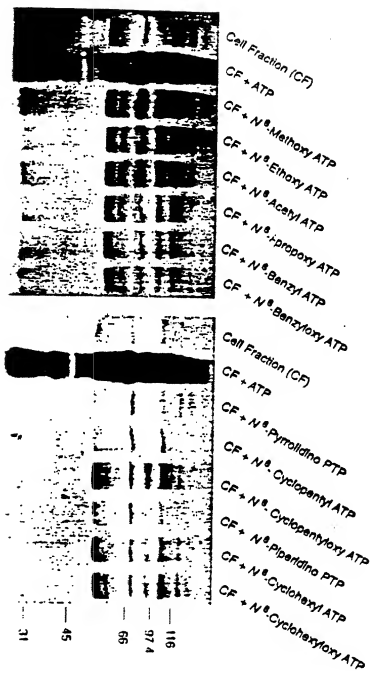


Figure 3

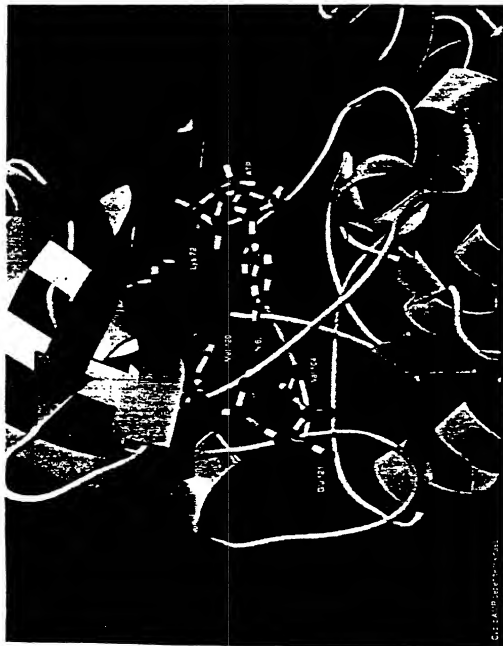


Figure 4

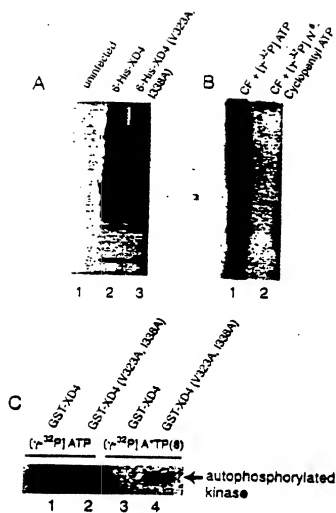


Figure 5

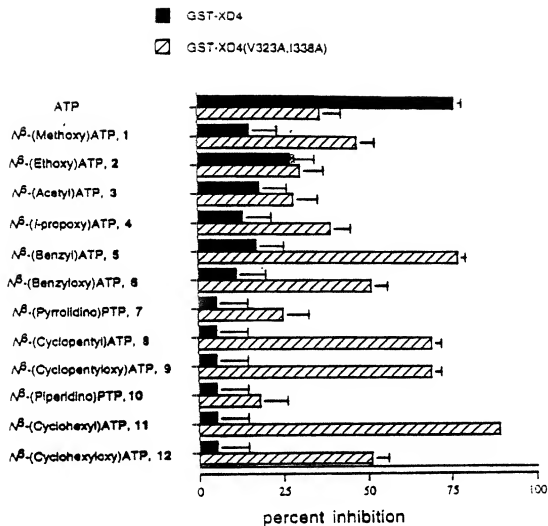


Figure 6

10044667-011502

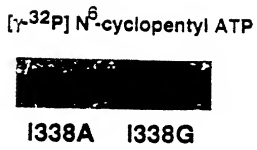
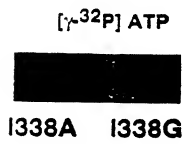
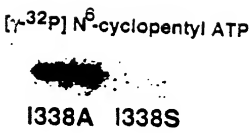
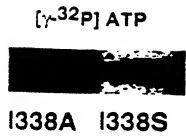


Figure 7

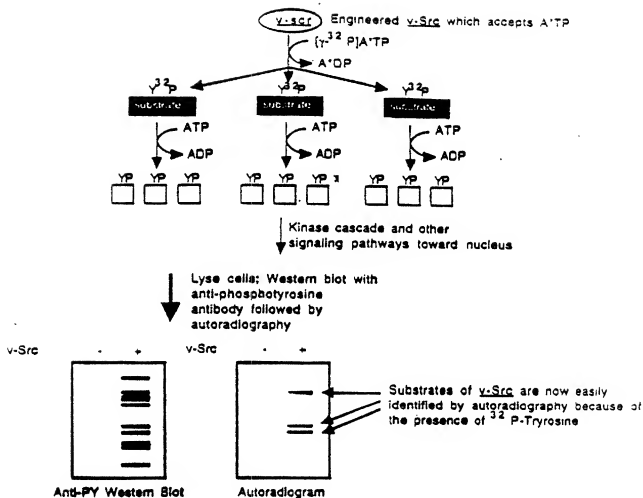
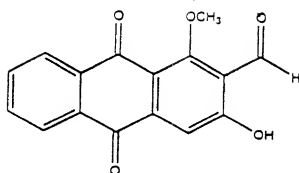


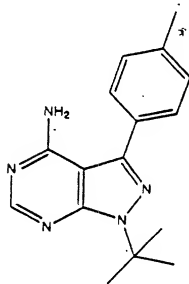
Figure 8

A. Damnacanthal



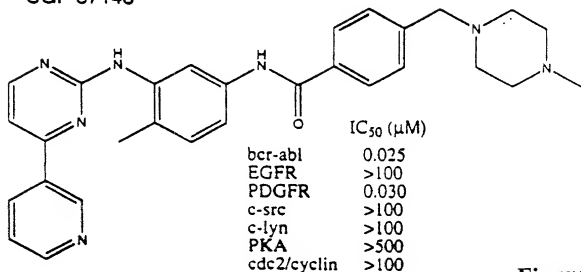
| | IC ₅₀ (μM) |
|-------|-----------------------|
| lck | 0.10 |
| fyn | 2.09 |
| src | 0.68 |
| erbB2 | 3.5 |

B. PP1



| | IC ₅₀ (μM) |
|--------|-----------------------|
| lck | 0.005 |
| fyn | 0.006 |
| src | 0.17 |
| hck | 0.020 |
| zap-70 | >100 |
| JAK2 | >50 |
| EGFR | 0.25 |

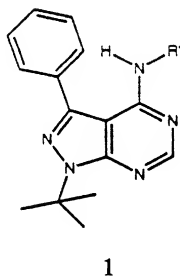
C. CGP 57148



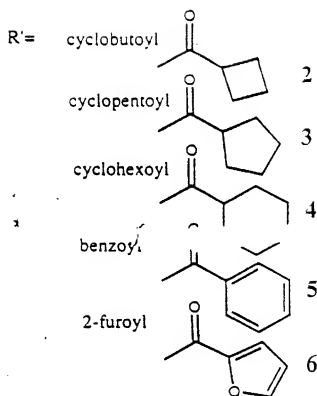
| | IC ₅₀ (μM) |
|-------------|-----------------------|
| bcr-abl | 0.025 |
| EGFR | >100 |
| PDGFR | 0.030 |
| c-src | >100 |
| c-lyn | >100 |
| PKA | >500 |
| cdc2/cyclin | >100 |

Figure 9

A. N-4 Acyl Analogues



B.



C. *In vitro* Inhibition Data

| R' | IC ₅₀ (μM) | | |
|--------------|-----------------------|--------|-----------|
| | WT fyn | WT src | I338G src |
| H | 0.08 | 35 | <1 |
| cyclobutoyl | | >>400 | 12 |
| cyclopentoyl | 400 | >>400 | 5 |
| cyclohexoyl | 50 | >>400 | 20 |
| benzoyl | >400 | >>400 | 50 |
| 2-furoyl | | >>400 | 150 |

Figure 10

A

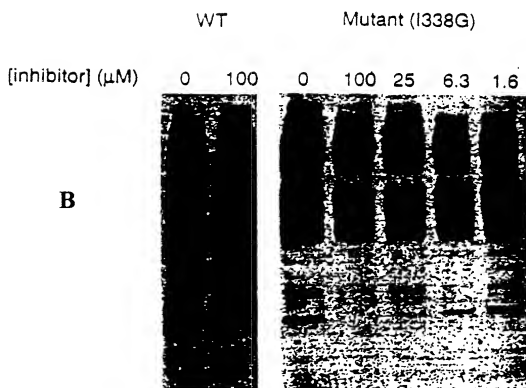
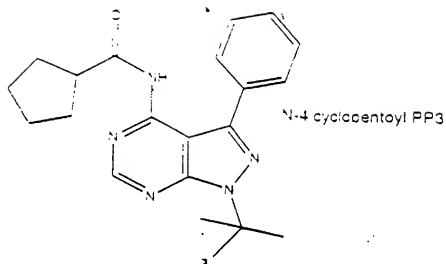


Figure 11

IC₅₀ (μM)










| | Molecule | WT XD4 | I338G XD4 | WT Fyn | T339G Fyn | WT Abl | T120A Abl |
|---|---|--------|-----------|--------|-----------|--------|-----------|
| a |  | 35 | 0.13 | 0.05 | | | <<10 |
| b |  | | 200 | >300 | | | |
| c |  | | 300 | >300 | | | |
| d |  | | >300 | >300 | | | |
| e |  | >300 | 75 | >300 | 100 | | >10 |
| f |  | >300 | 250 | >300 | 26 | | >10 |
| g |  | >300 | 85 | >300 | 63 | | >10 |
| h |  | | | | | | |
| i |  | | | | | | |

Figure 12A













| | | | | | | |
|---|---|------|--------|-----|------|---------|
| j |  | | | | | |
| k |  | | | | | |
| l |  | >300 | 12 | 6.5 | 5 | |
| m |  | >300 | 19 | 80 | 9 | |
| n |  | >300 | 20 | 50 | 5 | |
| o |  | >300 | 150 | 15 | 19 | |
| p |  | >300 | 10 | 300 | 11 | (10 |
| q |  | >300 | 10 | 300 | 6 | (10 |
| r |  | | 1.2 | | | <10 |
| s |  | | 0.63 | | | |
| t |  | | (0.411 | | | 1.8 |
| u |  | >300 | 0.43 | 300 | 0.83 | 300 (10 |

Figure 12B











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| v |  | | | | | |
| w |  | | | | | |
| x |  | | | | | >10 |
| | | | | | | |
| y |  | 100 | (0.05 | 0.1 | | |
| z |  | | >100 | >300 | | |
| aa |  | | | 2 | | |
| bb |  | | | 7 | | |
| | | | | | | |
| cc |  | | | | | |
| dd |  | | | | | |
| ee |  | | | | | |

Figure 12C











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|----|---|-------|-------|------|-------|--|
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| gg |  | | | | | |
| hh |  | | | | | |
| ii |  | | | | | |
| jj |  | | | 1 | | |
| kk |  | | | | | |
| ll |  | | | | | |
| mm |  | | | | | |
| nn |  | >1000 | 0.510 | 0.4 | <<6.5 | |
| oo |  | >300 | >10 | >300 | | |

Figure 12D










| | | | | | | | |
|----|---|------|-----|------|--|--|--|
| pp |  | >300 | >10 | >300 | | | |
| qq |  | >300 | >10 | >300 | | | |
| rr |  | >300 | >10 | >300 | | | |
| ss |  | >300 | >10 | >300 | | | |
| tt |  | >300 | >10 | >300 | | | |
| uu |  | >300 | >10 | >300 | | | |
| vv |  | >300 | >10 | >300 | | | |
| ww |  | >300 | >10 | >300 | | | |
| xx |  | >300 | >10 | >300 | | | |
| | | | | | | | |

Figure 12E

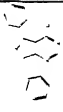
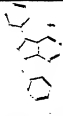






| | | | | | | |
|-----|---|------|-----|------|--|--|
| yy |  | | | | | |
| zz |  | <10 | 2.5 | <<10 | | |
| aaa |  | >300 | >10 | >300 | | |
| bbb |  | >300 | >10 | >300 | | |
| ccc |  | >300 | >10 | >300 | | |
| ddd |  | >300 | >10 | >300 | | |
| eee |  | >300 | >10 | >300 | | |
| fff |  | >300 | >10 | >300 | | |

Figure 12F

Figure 13A

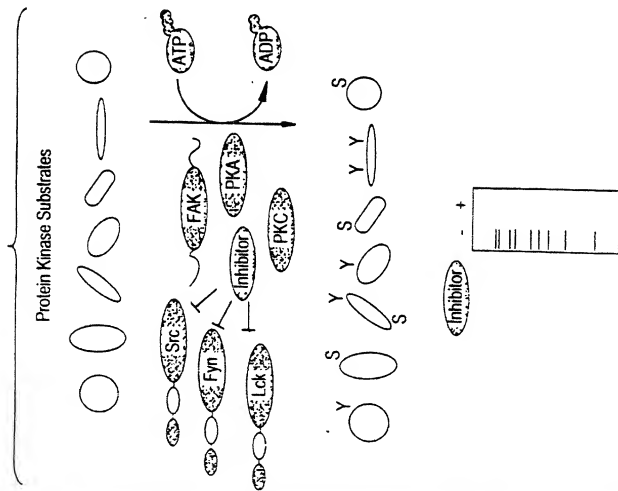
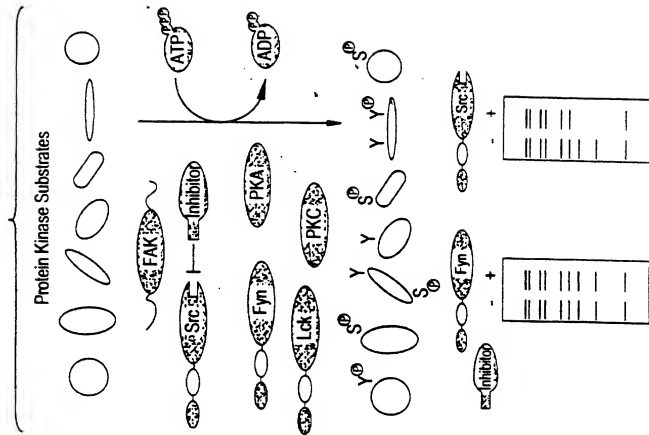


Figure 13B



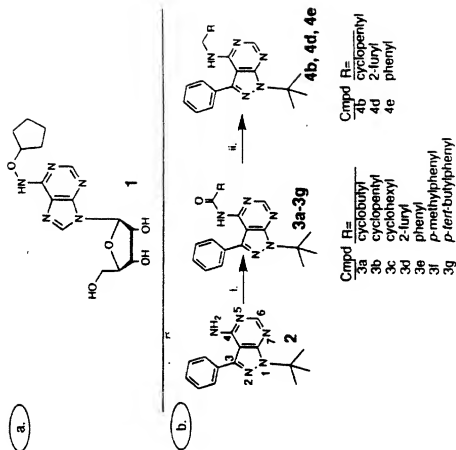


Figure 14

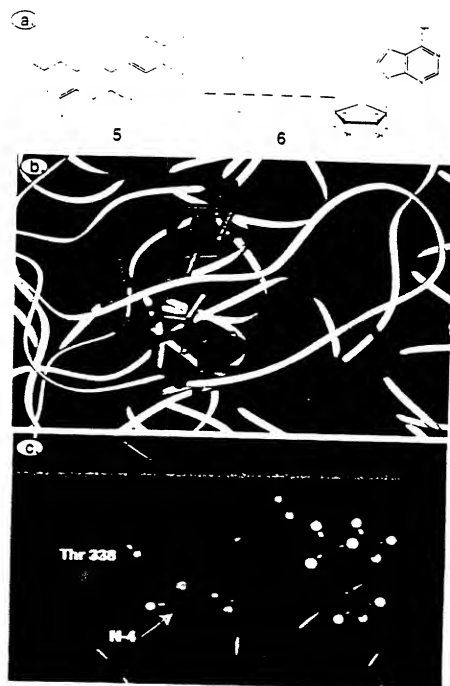


Figure 15

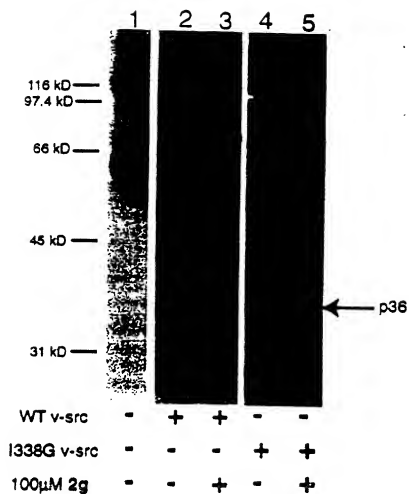


Figure 16

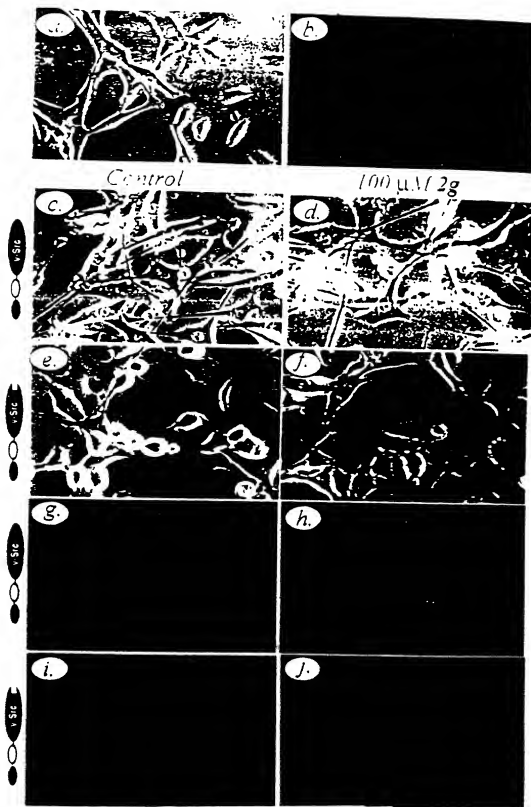
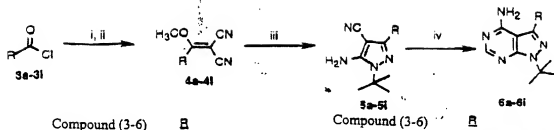
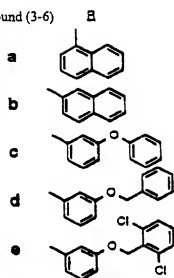


Figure 17



Compound (3-6)



Compound (3-6)

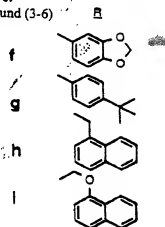


Figure 18

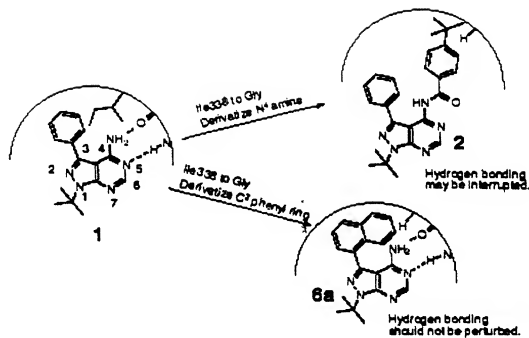


Figure 19

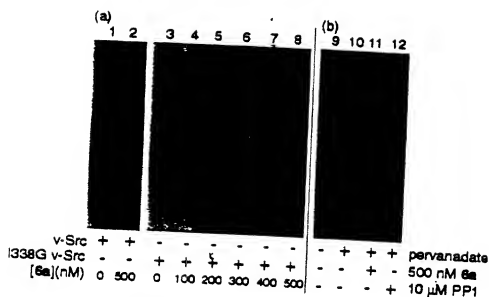


Figure 20

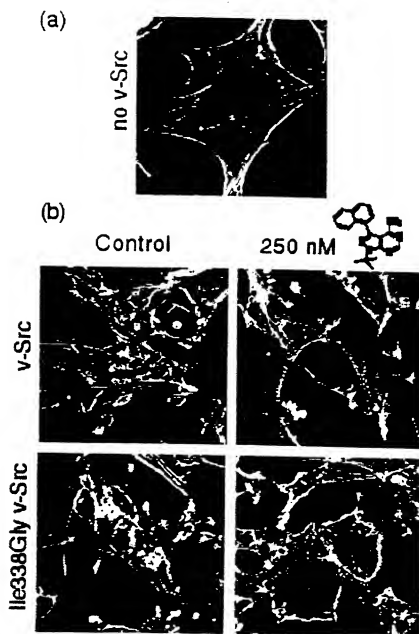


Figure 21

Figure 1

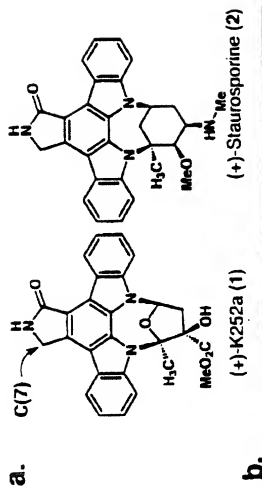


Figure 22

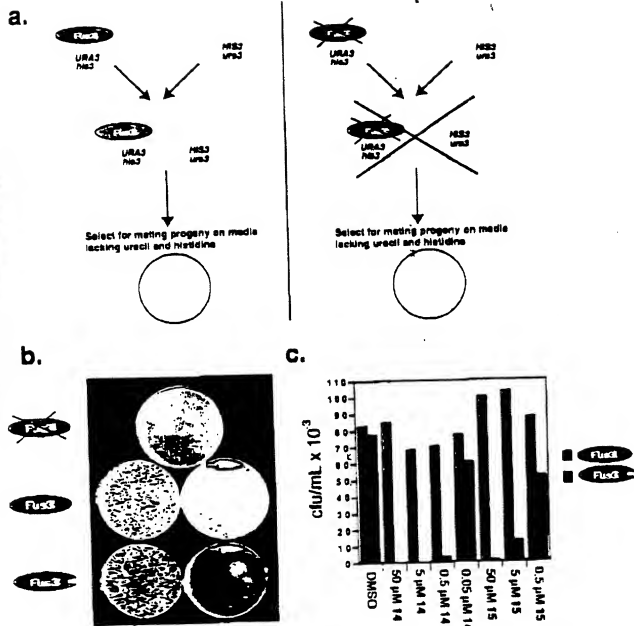


Figure 23

10044967.01502

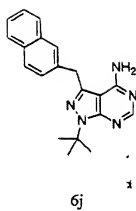
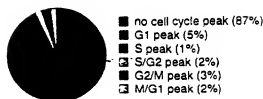
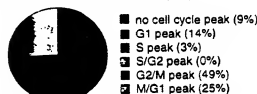


Figure 24

A All *S. cerevisiae* genes (6,200)

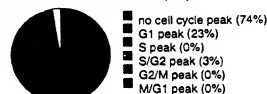


B Decreases - 120 min (66)



| Unreg | | S | M | G1 | M/G1 | | |
|---------|-------|-------|-------|---------|-------|---------|-------|
| AME1 | -3 | HTB2 | -4.8 | PHO3 | -21.5 | | |
| BAR1 | -5.1 | MET14 | -5.8 | PHO5 | -10.5 | AG24 | -5.9 |
| PUT4 | -3.2 | | | PRY1 | -3.2 | ICG2 | -9.3 |
| BURA | -4.1 | G2/M | | SDL1 | -3.8 | GYM6 | -2.5 |
| YER077C | -5.5 | ALK1 | -3.5 | RPI1 | -2.7 | FAA2 | -4.7 |
| YER067W | -5.5 | ATP2 | -6.1 | SEN1 | -3.5 | IAN2 | 3.4 |
| G1 | | BHS1 | -3.7 | STE2 | -2.5 | ICA4 | -4.7 |
| CTB1 | -28.4 | COC20 | -4.1 | STE6 | -4.8 | NCM3 | |
| GPM1 | -2.5 | CLB2 | -4.1 | SUR7 | -2.5 | PCL8 | 4.9 |
| MPH1 | -3.2 | DBP2 | -3.8 | SWR5 | -3.1 | PRI1 | 3.7 |
| PTP2 | -2.7 | FAR1 | -25.4 | YOR032W | -15.8 | PTB1 | 2.5 |
| RME1 | -2.1 | HST3 | -4.1 | YVL159W | -4.8 | SPH1 | -7.6 |
| RMC10 | -41.2 | MPA2 | -4.8 | YVL561W | -4 | YNL049W | -3.7 |
| SCW11 | -18.4 | MYO1 | -3 | YVL284C | -4.3 | YNR057C | -19.4 |
| YER124C | -4.8 | PHO11 | -4.8 | YML119W | -4.1 | YOR061W | -3.7 |
| YHR121W | -2 | PHO12 | -4.8 | YML266C | -3.1 | YOR124W | -2.7 |
| | | | | YRA2 | -7.8 | YPL185C | -4.6 |

C Increases - 120 min (38)



| Unreg | | | G1 | S/G2 | |
|-------|-----|-----------|------|---------|-----|
| BIO3 | 2.8 | YAR069W | 4.5 | CLB2 | 2.3 |
| DIC1 | 2.9 | YBR041C | 3.7 | CSE2 | 3.2 |
| ERR1 | 2.2 | YCR059C | 2.8 | PCL1 | 4.7 |
| GSC2 | 2.5 | YEL019W | 3 | PRY3 | 2 |
| CUT5 | 2.8 | YFL041W | 3.2 | SMO4 | 2.8 |
| HEM19 | 2.8 | YGL041W | 2.8 | YLL012W | 2.8 |
| MAL1 | 4.1 | YGL170C | 3.8 | YLL235W | 4 |
| MRP20 | 2.7 | YHR119W-A | 2.8 | YNL330W | 2.8 |
| HQR1 | 2.5 | YIL185C | 26.1 | YPS4 | 2.4 |
| PES4 | 3.1 | YLR043C | 6.1 | | |
| SKM1 | 2.7 | YMR123C | 2.7 | | |
| SPD11 | 3.8 | YMR127W | 3.5 | | |
| THI12 | 2.8 | YOR043C | 3.3 | | |
| THI21 | 2.5 | YPL230W | 3.1 | | |

D Genomic trends

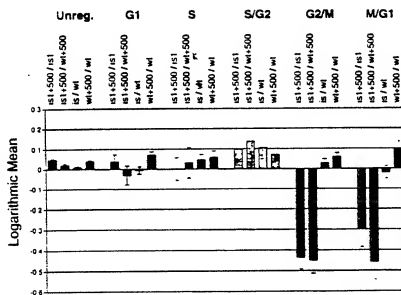


Figure 25

a.

| Protein/Kinase | Kinase Family | Specificity | Cellular Function |
|----------------|------------------------------|-------------|---|
| v-Src | Src | Tyr | oncogenic transformation |
| c-Fyn | Src | Tyr | lymphocyte activation |
| c-Abl | Abl | Tyr | F-actin binding, transcription |
| CAMK II | calcium/calmodulin dependent | Ser/Thr | long-term potentiation, memory |
| CDK2 | cyclin dependent | Ser/Thr | mammalian cell cycle progression |
| CDC28 | cyclin dependent | Ser/Thr | <i>S. cerevisiae</i> cell cycle progression |
| Fus3 | mitogen-activated | Ser/Thr | <i>S. cerevisiae</i> mating |

b.

| | |
|---------|--|
| v-Src | (318) RHEKLVQLYAMVSE-----EPYIVIVIEYMSK--GSLLDPLKGMCKY |
| Fyn | (319) KHOKLVOLYAVVSE-----EPYIVIVIEYMSK--GSLLDPLKDGEGRA |
| Abl | (294) KHPNLVQLLGVCVTR-----PPFYIITEPMTY--GNLLDYLRECNQEE |
| CamK II | (68) KHPNIVRLHDSISSE-----GHYLIIFDLVVG--GELFDIVAREY |
| Cdk2 | (59) NHPNIVKLVDIINTE-----NKLVLVFEFLHQ---DLKKPMDSALTG |
| Cdc28 | (66) KDNIVRLYDIVHSDA-----HKLVLVFEFLDL---DLKRYMEGIPKDDP |
| Fus3 | (67) KENIITIFNIQRPSFENF-----NEVYIIQELMOT---DLHRVISTQM |

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Figure 26

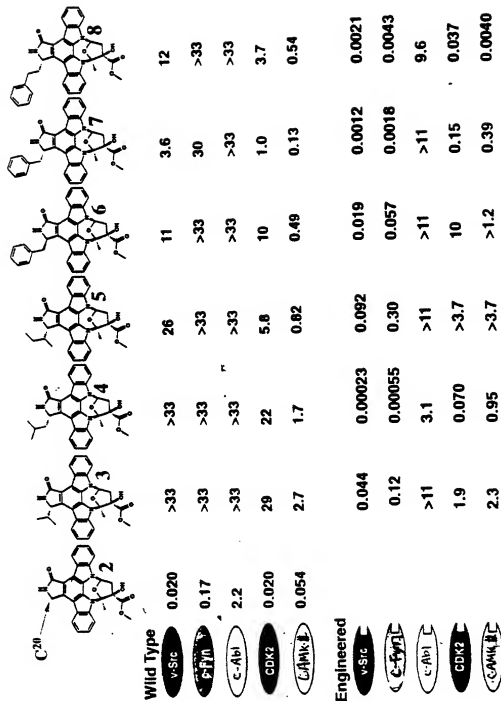


Figure 27

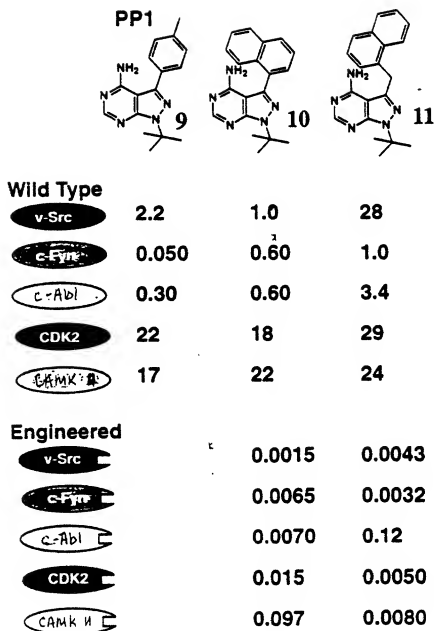


Figure 28